AUSTRALIA

Patents Act 1990

IN THE MATTER OF
US Patent Application No. 09/582,059
by Jackson & Subasinghe, assigned to
MONASH UNIVERSITY &
POLYCHIP PHARMACEUTICALS
PTY LTD

STATUTORY DECLARATION

I, William Roy Jackson of 30 Through Road, Burwood, Victoria, 3125, Commonwealth of Australia, do solemnly and sincerely declare as follows:

1. I am the Sir John Monash Distinguished Professor of Chemistry and Director of the Australian Research Council Centre for Green Chemistry at Monash University, Melbourne, Australia, and I am one of the inventors of the above-identified application.

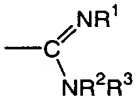
2. I hold the degrees of B.Sc.(Hons) from the University of Manchester, and Ph.D. and D.Sc. from King's College London, I am a fellow of the Royal Australian Chemical Institute, The Australian Institute of Energy, and the Australian Academy of Technology and Engineering. A copy of my *curriculum vitae* is annexed hereto as Exhibit WRJ-1.

3. I have read and understood the Office Action dated 5 December 2001 issued in respect of this application. In particular, I have read the rejections under section 102(b) and section 103(a) which the Examiner has made on the basis of the paper entitled "Chemical Design of Peripherally Acting Compounds" by Jackson et al published in Clinical and Experimental Pharmacology and Physiology (1992) 1917-73, of which I am the first author. As stated on the first page of the reference, this paper was presented at a symposium in honour of Professor Alan L A Boura, Professor of Pharmacology at Monash University, on the occasion of his retirement, which was held at Monash University on 28 June 1991.

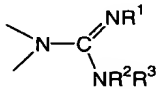
4. The paper described attempts to design compounds which were unable to pass through the blood-brain barrier, and which therefore exert their pharmacological effects only in the periphery and not in the central nervous system (CNS). It was sought to achieve this by attachment of a strongly basic guanidino group to the parent compound, because it was known that biologically active molecules with highly polar or ionic functional groups cannot penetrate the blood-brain

barrier. Modification of two drugs, mianserin and morphine, was described.

5. In 1988, Professor Boura, Dr Frederick Copp, Dr John Cullen and myself had investigated the introduction of strongly basic functionalities, namely amidines (1) and guanidines (2)



(1)

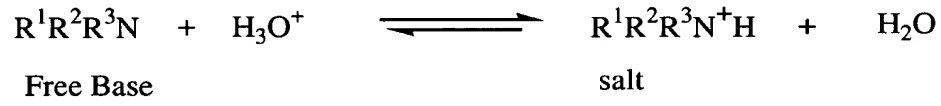


(2)

into pharmacologically active molecules. This work is described in US Patent No. 5049637. The inclusion of such groups into molecules means that at physiological pH a high percentage of such groups would have reacted with the acidic protons to form salts. Thus, the equilibrium shown below would lie far to the right:

Free Base

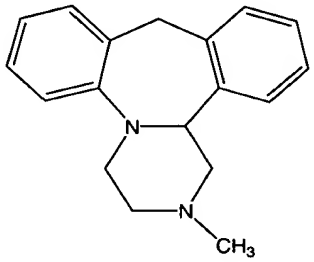
The equilibrium constant, i.e. the measure of how far the species on the right-hand side of the equation are favoured over those on the left-hand, is usually expressed as pKa; the larger the value of pKa, the stronger the base. The pKa values for the very basic guanidines are approximately 16 and for amidines are approximately 12. Amines themselves are also basic, but their basicity is much less than that of amidines and guanidines, with pKas of 10-11 for most alkylamines, and thus the equilibrium lies much more to the left, and significant amounts of free base will be present:



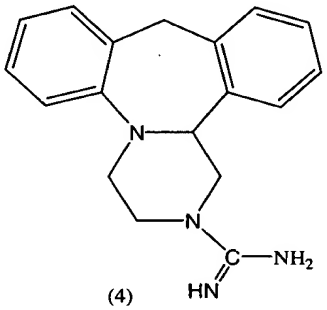
Free Base salt

6. The blood-brain barrier is lipophilic i.e. has an affinity for fatty materials rather than water-like materials, and it does not readily allow salts, which are hydrophilic (water-loving) to pass through. It is thus in principle possible to prepare compounds which cannot pass the blood-brain barrier, and whose activity is only available to peripheral and not to CNS-based body functions.

7. We applied this methodology to mianserin (3), a compound which was known to have both anti-histamine and sedative activity. In our US Patent No. 5049637 the guanidino derivative (4) was shown to retain its anti-histamine activity but not to be sedative, and thus was probably not gaining access to the CNS.



(3)



(4)

8. We then decided to apply this principle to the modification of opioid activity. Many opioids are excellent analgesics, but they usually have adverse effects associated with their interactions with the CNS. It was thought that the protonated guanidino or amidino substituents would prevent access to the blood-brain barrier, and that the compounds would retain peripheral analgesic action with no CNS effects.

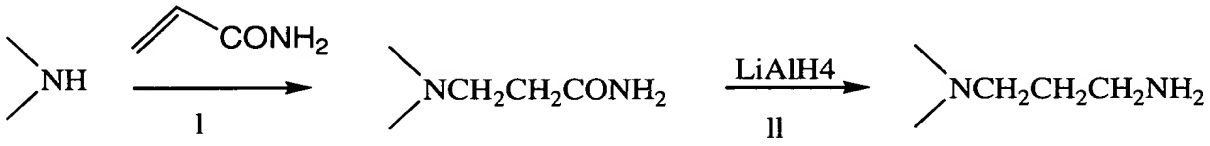
9. However, the one compound that we prepared, which had yielded only a very small amount, proved not to be an effective analgesic, and there was evidence that the compound was acting in the CNS. Professor Boura, who was in charge of the pharmacological testing, convinced me at that time that the outlook for the project was very unpromising, and as no further funding was available the project was abandoned in 1992.

10. A brief note summarising the initial poor findings was included in the paper by Jackson et al., which was written for the symposium held to mark Professor Boura's retirement.

11. The "further testing" referred to at page 23 column 1 of the Jackson et al paper, which had been performed using the limited amounts of compound then available, had confirmed the lack of activity. The "breakdown in the body" referred to at page 23 column 1 refers to removal of protecting groups from the body; because of the CNS activity which had been observed in the initial experiments, we did not consider that it was worthwhile preparing a deprotected compound and then treating animals to evaluate whether or not there was CNS activity, because our results suggested that in fact such activity was present.

12. Dr Kamani Subasinghe, the other inventor in respect of this application, joined my

laboratory in 1995. In 1996, in connection with an unrelated project, we attempted to repeat the reactions which formed an essential part of our synthesis of the compound reported in Jackson et al.



We faced enormous difficulty in obtaining the target compounds using reactions (I) and (II). In support of this, I annex hereto as Exhibit WRJ-2 copies of documents prepared during the course of these experiments which show that we were unable to prepare compound (23) referred to in the Jackson *et al* paper. I therefore wondered whether the reactions leading to the compound reported in Jackson et al had proceeded badly, and that an impure sample had in fact been prepared. Limited analytical data was available for the compound, as only a small amount was prepared, the grant funding had ceased and the pharmacological studies were highly negative.

13. Our re-evaluation revealed that some of the synthetic steps were causing difficulty, and as a result of these difficulties in synthesis and the poor yield and purity there was some doubt as to whether the compound described in the paper by Jackson *et al* was in fact even present. Even if it was, which I cannot be sure of, certainly it was not pure, and there were major contaminants. Moreover, there was evidence that whatever compounds were present in the earlier preparation did penetrate the CNS.

14. We devised a novel method of synthesis. This method gave much better yield and purity. This method involved the use of acrylonitrile to prepare the precursor compound referred to as (21) at page 22 of the paper by Jackson et al, rather than acrylamide, as in the Jackson et al paper. A different method was also used for the step of conversion of compound (22) to compound (23). The tributylsilyl-protected compound (23) was made using this modified synthesis and then deprotected; however, the deprotected compound was not only active, but was found not to penetrate the CNS to any significant extent.

15. In view of our new findings I decided that the project was worthy of further investigation, and persuaded Polychip Pty Ltd to fund a reinvestigation of the synthesis and pharmacological evaluation of this series of compounds. The new project commenced on 3 October 1996.

16. We had only undertaken the resynthesis and retesting because even if there is a degree of CNS activity, the compounds are potentially useful as analgesics. However, such compounds are much more useful if there is little or no CNS activity.

17. Dr Subasinghe and I had to overcome significant difficulties in order to prepare the compound, in a sufficient degree of purity, in order to be able to carry out tests on whether the compound had any activity, and whether it penetrated the CNS. In order to do so, we had to change the previously-published synthesis in two significant separate ways.

18. It was only because we had unexpectedly discovered that we could not repeat the synthesis and the compound previously tested was probably not the compound reported to be present, or at best was extremly impure, that we even contemplated repeating this work.

19. The findings that the free guanidino compound was active, and has activity only in the periphery, were completely unexpected in the light of the original results which had been reported in the paper by Jackson et al.

AND I MAKE this solemn Declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by the Act for the making of false statements in Statutory Declarations, conscientiously believing the statements contained in this Declaration to be true in every particular.

DECLARED at Melbourne this 22nd day of May 2002

William Roy Jackson

William Roy Jackson

Before me: at Clayton, Victoria 3168
22nd May 2002

Eva Campi

A person empowered to witness Statutory Declarations under the laws of the State of Victoria, Commonwealth of Australia

EVA CAMPI (Pharmacist)
123A Abbott St
Sandringham 3191

COMMONWEALTH OF AUSTRALIA

Patents Act 1990

IN THE MATTER OF
Patent Application No. 09/582,059 by Jackson & Subasinghe, assigned to MONASH UNIVERSITY & POLYCHIP PHARMACEUTICALS PTY LTD

EXHIBIT WRJ-1

This is Exhibit WRJ-1 referred to in the Statutory Declaration by William Roy JACKSON

dated 22nd May 2002

William Roy Jackson

Before me: at Clayton, Victoria, 3168
22nd May 2002

Eva Campi

EVA CAMPI (Pharmacist)
123A Abbott St
Sandringham 3191

A person empowered to witness Statutory Declarations under the laws of the State of Victoria, Commonwealth of Australia

CURRICULUM VITAE

William Roy Jackson, Sir John Monash Distinguished Professor
Chemistry Department, Monash University, Clayton, Vic. 3168.

DATE AND PLACE OF BIRTH:

27th February, 1935, Bacup, Lancashire, England, U.K.

DEGREES:

B.Sc. Manchester (1st class Hons.) 1955, Ph.D. Kings College, London University 1958, D.Sc. London University, 1973.

HONOURS & AWARDS:

Fellow of the Royal Australian Institute of Chemistry, President 2000

Fellow the Australian Institute of Energy

1985:	Joint winner (with Prof. F.P. Larkins) of Sir Ian Wark Applied Research Medal of R.A.C.I.
1990:	Fellow of the Australian Academy of Technological Sciences and Engineering.
1991:	Winner H G Smith Memorial Medal of R.A.C.I. for Pure Research in Chemistry
1992	Joint winner (with Prof. F.P. Larkins) Baragwanath Award of Australian Institute of Energy

EMPLOYMENT:

1958-59:	US Ethyl Corporation Postdoctoral Fellow at Oxford University with Professors E.R.H Jones, F.R.S. and M.C. Whiting.
1959-62:	Assistant Lecturer, Queen's University of Belfast.
1962-70:	Lecturer in Organic Chemistry, Queen's University of Belfast.
1970-72:	Reader in Chemistry, Queen's University of Belfast.
1973 - present:	Professor of Organic Chemistry, Monash University, (Head of Dept. 1992 - 1994)
1995	Sir John Monash Distinguished Professor
2000	Director, Centre for Green Chemistry

RESEACH FUNDING:

- Major grants from industry and government in excess of $10,000,000
- Extensive cooperation with Australian industry in research collaboration and contract research including ICI Australia, Amrad, Kemcor, Wooltech (a Consolidated Press subsidiary), Nufarm and Daratech.

RESEARCH INTERESTS:

Catalysis in Organic Synthesis

The development of new catalyst systems for organic chemical reactions with particular emphasis in obtaining good regio- and stereoselectivity. Many, but not all of the catalytic systems have been based on organometallic compounds. New asymmetric catalysts for the preparation of organic molecules with significant biological activity have been developed.

Clean Energy from Victorian Brown Coal:

A long-standing interest in brown coal utilisation arose from initial projects aimed at liquid fuel production. This interest in coal structure and coal reactivity has led to involvement with the CRC for Clean Power from Lignites into methods for improving the control of greenhouse gas emissions. In addition agricultural applications of brown coal and brown coal products are being studied in collaboration with HRL Pty Ltd.

New Materials

Development of new materials with applications in the areas of pharmaceuticals, controlled release of biologically active compounds, polymer attached liquid crystals for optoelectronic devices.

Green Chemistry

As Director for the Centre for Green Chemistry, I have overall responsibility for some 15 projects (annual budget > $1 million). Work on the development of new 'green' routes to latexes (with Dulux Pty Ltd) and evaluation of non-phosgene based routes to isocyanates (for the preparation of polyurethane) have been initiated by me and further external funding obtained.

RESEARCH APPLICATIONS

Much of the above research has involved industrial collaboration and has led to patents in several areas. Nufarm are currently operating a pilot plant to prepared large quantities of the water-dispersable powder formulation of the herbicide, trifluralin for evaluation in the American wheat market. Amrad are currently investigating the possible commercialisation of a neuroprotective drug and Polychip Pharmaceuticals a non-addictive opiod analgaesic. Both compounds have arisen from work carried out by us and are the basis of joint patents with the companies.

EXPERT WITNESS

Professor Jackson has acted as an expert witness in several cases involving major pharmaceutical companies.

PUBLICATIONS:

- Over 300 publications in refereed journals. Seven international patents.
- Ten seminal publications

1. J.-L. Chen, P.A. Horne, W.R. Jackson, G. Lichti and D. Park, "Volatility control for foliage-applied chlorpyrifos by using controlled release emulsions", *Journal of Controlled Release*, 1994, **29**, 83-95.

2. K.J. Coutinho, R.S. Dickson, G.D. Fallon, W.R. Jackson, T. De Simone, B.W. Skelton and A.H. White, "Isolation and characterisation of hydroformylation intermediate from stoichiometric reactions between phosphinoalkenes and some heterobinuclear complexes", *J. Chem. Soc.*, Dalton, 1997, 3193-3199.

3. W.R. Jackson, J.R. Anderson, E.M. Campi, Ciptati, Q.J. McCubbin and Z.-P. Yang, "Three approaches to catalytic aqueous organometallic chemistry involving water soluble ligands, some modified cyclodextrins as ligands, and reactions in an aluminophosphate cavity", in *Aqueous Organometallic Chemistry & Catalysis* (Eds. I.T. Horváth and F. Joó), 1995, 187-194.

4. R.F.C. Brown, A.C. Donohue, W.R. Jackson and T.D. McCarthy, "Synthetic applications of optically active cyanohydrins. Enantioselective syntheses of the hydroxyamides Tembamide and Aegeline, the cardiac drug Denopamine, and some analogues of the bronchodilator Salbutamol", *Tetrahedron*, 1994, **50**, 13739-13752.

5. E.M. Campi, W.R. Jackson, S.M. Marcuccio and C.G.M. Naeslund, "High yields of unsymmetrical biaryls *via* cross coupling of arylboronic acids with haloarenes using a modified Suzuki-Beletskaya procedure", *J. Chem. Soc., Chem. Commun.*, 1994, 2395.

6. W.R. Jackson, F.C. Copp, J.D. Cullen, F.J. Guyett, I.D. Rae, A.J. Robinson, H. Pothoulackis, A.K. Serelis and M. Wong, "Chemical design of peripherally acting compounds", *Clinical and Experimental Pharmacology and Physiology*, 1992, **19**, 17-23.

7. W.R. Jackson and F.P. Larkins, "Chapter 10: Hydrogenation & Reduction" in 'The Science of Victorian Brown Coal. Structure, Properties and Consequences for Utilisation', Ed. R.A. Durie, Butterworth-Heinemann, Oxford, 1991.

8. P.J. Cassidy, W.R. Jackson, F.P. Larkins, M. B. Louey and R.J. Sakurovs, "Promoters for the liquefaction of wet Victorian brown coal in carbon monoxide", *Fuel Processing Technology*, 1986, **14**, 231-246.

9. P.J. Redlich, W.R. Jackson and F.P. Larkins, "Hydrogenation of brown coal: (9) Physical characterisation and liquefaction potential of Australian coals", *Fuel*, 1985, **64**, 1383-1390.

10. B. Jarrott, P.M. Beart, V.J. Kenche, A.D. Robertson and M.P. Collis, "Arylalylpiperazine Compounds as Antioxidants" International Pat. Appl. PCT/AU97/00293.

Patents Act 1990

IN THE MATTER OF
Patent Application No. 09/582,059 by
Jackson & Subasinghe, assigned to
MONASH UNIVERSITY &
POLYCHIP PHARMACEUTICALS
PTY LTD

EXHIBIT WRJ-2

This is Exhibit WRJ-2 referred to in the Statutory Declaration by William Roy JACKSON

dated 22nd May 2002

William Roy Jackson

Before me: at Clayton,
Victoria 3168
22nd May 2002

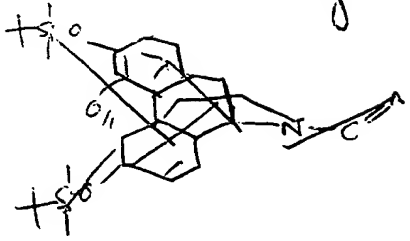
Eva Campi

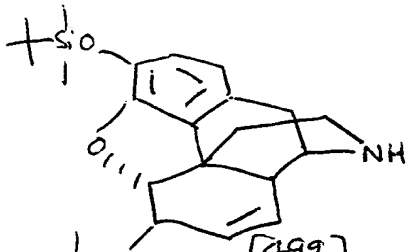
EVA CAMPI (Pharmacist)
123A Abbott St
Sandringham 3191

A person empowered to witness Statutory
Declarations under the laws of the State of
Victoria, Commonwealth of Australia

6/11/96

Ref: John G. Erickson.
J. Am. Chem. Soc. 1952, 74, 6251





[499]
[KRS-16]
0.2g.

$CH_2=CHCONH_2$.

KRS-20.
— No reaction —
[520]

0.00060 mol.

acrylamide 0.00066 mol. = 0.050 g.
Methanol. 5 mL.

A mixture of KRS-16 and acrylamide in 5 mL methanol was stirred at room temperature ~~The white precipitate was filtered and dissolved in water and the free base was liberated from with K_2CO_3~~ for overnight. After stirring for

Overnight the reaction mixture was evaporated and (MeOH was removed) analyzed by TLC & NMR. TLC & NMR showed the starting material. No reaction has occurred.

3/11/97

KB-2-29-2

0.16 g

0.00032 mol

in 3 mL MeOH

+ $CH_2CH_2CONH_2$ .00032 mol, 0.0227 g

→ Stirred at RT → no reaction.

Same reaction was repeated but stirred for 2 days at room temp under N_2. Still no reaction. Starting material was isolated. (From TLC & NMR).

no reaction.

but up

5/21/17.

KRS-2-29-2. + $CH_2=CH_2-CONH_2$ ——→ no reaction

(499)

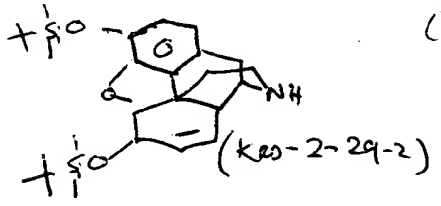
0.08g 0.0125g.

3mL MeOH.

Stirred at room temperature.

0.16m mol. 0.17 m.mol

(1.1g)



(KRS-2-29-2)

A mixture of KRS-2-29-2 and acrylanide in 3mL Methanol was stirred at room temp overnight. After overnight no change on TLC. The reaction mixture was evaporated and analysed by NMR. NMR was similar to starting material (KRS-2-29-2). ∴ No reaction.

KR-2-2

0.56 g

0.0019 mol

5 mL CH_2Cl_2

2 ml Ac_2O

Et_3N . 5 mL

DMAP

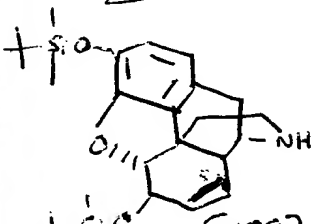
RT 1h

10-2-97

Ref: J.C. Erickson JACS Vol 74 (6281-82), 1952

KR-30-1

0.38 g



(499)

0.00076

$CH_2=CHCONH_2$

KR-30-2

570

acryl amide (1.5eq) 0.00114 mol = 0.08 g

MeOH = 5 mL

Stirred at room temperature for 2 days. (No Change on TLC)

BATCH An additional 0.08 g of acrylamide was added and stirred at room temperature. Still no reaction. Starting material was isolated.